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Letter to the Editor

Reply

We acknowledge Dr. Padera *et al.* (1) for their constructive comments on our recent article "Intratumoral lymphatics are essential for the metastatic spread and prognosis in squamous cell carcinomas of the head and neck region" by Maula *et al.* (2) and appreciate the chance to respond. In consideration of the fact that the prognostic capacity of lymphatic markers in cancer is still under active investigation, Dr. Padera points out that the use of the word essential in the title of our article overstated the likely importance of IT[1] vessels in the metastatic process.

Recently, there has been much debate, discussion, and controversy in scientific reports about the occurrence and functional role of IT lymphatics. It is now evident that proliferating IT lymphatics are indeed present in cancers such as head and neck carcinoma and that their presence is at least associated with nodal metastasis (3) if not absolutely essential for the process. Padera *et al.* hold the general view that IT lymphatics are by definition nonfunctional and cannot contribute to nodal metastasis (4). In the article by Maula *et al.* (2), we studied a population of 97 patients diagnosed with squamocellular carcinoma of the head and neck region. We showed that IT LYVE-1-positive lymphatics were strongly associated with nodal metastases and poor prognosis, whereas juxtatumoral LYVE-1-positive vessels showed quite the opposite correlation. In their letter, Padera *et al.* (1) correctly point out that IT LYVE-1+ lymphatics were identified only in 9 of 38 patients with nodal involvement. However, the difference in the survival of these patients was striking when compared with patients without LYVE-1-positive IT lymphatics insofar as 7 of 9 IT+ died of the disease, whereas only 10 of 40 PT+ died during the follow-up period. Of course it is possible and even likely that routes other than LYVE-1-positive IT lymphatics may also lead to lymphatic spread in HNSCC. As we stated in our article, "These results confirm earlier findings that IT lymphatics are present in HNSCC and further strengthen the suggestion that IT vessels act as a conduit for nodal metastasis." We did not imply that IT lymphatics were the only such conduit. Hence, we concede that the title but not the content of our article may have been misleading. In conclusion, we would stress that the lymphatic marker used both in our own study of HNSCC and in recent studies by Padera *et al.* carries the limitations of any so-called lineage-specific marker. However, it is our view that its application will be of a positive rather than a negative benefit in understanding the true role of tumor lymphatics in cancer.

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Correspondence re: H. Barthel *et al.*, 3′-Deoxy-3′-[^{18}F]fluorothymidine as a New Marker for Monitoring Tumor Response to Antiproliferative Therapy *in Vivo* with Positron Emission Tomography. Cancer Res., *63:* 3791–3798, 2003.

Letter

In the interesting study, Barthel *et al.* (1) compared FLT[1] with 2-[18F]fluoro-2-deoxy glucose as markers for the evaluation of antiproliferative therapy (5-FU) in mice. In agreement with other studies, a strong correlation between FLT and proliferation was seen in their study expressed as proliferating cell nuclear antigen index (2–5). They also reported that the drug-induced reduction of tumor uptake was more pronounced with FLT than with 2-[18F]fluoro-2-deoxy glucose.

In this letter, we would like to raise three issues. First, serum thymidine can compete with FLT for nucleoside carrier proteins and can therefore have influenced the results of their study. In extrapolation of FLT data from animal studies to human studies, the competition of endogenous thymidine with FLT must be taken into account. In mice and rats, serum thymidine levels are 9–15 times higher than in humans (6), which will result in a competition between FLT and serum thymidine for tissue uptake mechanisms. However, the high serum levels of thymidine in rodents can be lowered by administering i.v. thymidine phosphorylase before injection of FLT. Our preliminary results in a rat model show a 2.5-fold increase in tumor/muscle ratio of thymidine phosphorylase pretreated rats as compared with untreated control rats. Second, thymidine phosphorylase pretreatment might eliminate the mechanism (or one of the mechanisms) responsible for the discrepancy between TK_1 levels and FLT-uptake after 48 h (Figs. 2 and 3 in Ref. 1). Future animal studies with FLT in rodents should take the effect of serum thymidine into account and

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[1] The abbreviations used are: IT, intratumoral; HNSCC, squamous cell carcinoma of the head and neck; PT, peritumoral.

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[1] The abbreviations used are: FLT, 3′-deoxy-3′-[^{18}F]fluorothymidine; 5-FU, 5-fluorouracil.

should try to eliminate this effect by administering thymidine phosphorylase before injection of FLT.

Finally, we would like to add that the observed drug effects on FLT uptake in the mice model cannot be extrapolated to antiproliferative therapy in general as has been demonstrated by Dittmann *et al.* (7). They tested four types of chemotherapy: 5-FU; cisplatin; methotrexate; and gemcitabine. They found comparable results for 5-FU as those described in the study of Barthel *et al.* (1). However, after cisplatin treatment, FLT-uptake was increased rather than decreased after 72 h. Thus, different forms of chemotherapy can have completely different effects on the tumor uptake of FLT.

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